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(57) Abstract

Drugs that would benefit from sustained release at a controlled rate for an extended period of time in the stomach or upper intestinal tract are formulated in delivery systems that include a water-swellable particulate matrix impregnated with the drug combined with a chemical agent that pharmacologically induces the fed mode in the patient's stomach. By virtue of this combination, the drug can be ingested independently of the timing of the patient's food intake, and the drug matrix will be retained in the patient's stomach as a continuously dispensing reservoir of the drug even though the particulate matrix as ingested is not large enough to be retained in the patient's stomach other than when the stomach is in the fed mode.

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GASTRIC-RETENTIVE ORAL CONTROLLED DRUG DELIVERY SYSTEM WITH ENHANCED RETENTION PROPERTIES

This invention is in the general field of pharmacology, and relates in particular to formulations that provide drugs with controlled release and that are retained in the stomach for a prolonged period of time.

BACKGROUND OF THE INVENTION

Many drugs have been formulated to produce delivery of a drug at a continuous, controlled rate by sustained release of the drug into the digestive or circulatory system. Included among the advantages of sustained release are a reduction in the side effects of the drug, and the ability to achieve the effects of the drug with less frequent administration. Sustained release in the stomach offers further advantages, particularly in the treatment of local disorders of the stomach. Thus, the treatment of esophageal reflux disease, the eradication of ulcer-causing bacteria in the gastric mucosa, and the need for sustained antacid action all benefit from sustained drug release in the stomach. Sustained release in the stomach also enhances the absorption of agents that are not readily absorbed, by prolonging their time of contact at absorption sites in the stomach or the upper part of the small intestine where the absorption area or contact time is normally limited. Under normal conditions, material passes through the small intestine, for example, in as little as 1.3 hours, and this time becomes critical for agents, such as captopril and the cephalosporins, that are absorbed almost exclusively at this site. To be effective, these drugs must be administered either by injection or in frequent oral doses. A delivery system for these drugs that is retained in the stomach for a prolonged period of time, however, feeds the drugs to the small intestine in a continuous and prolonged manner, thereby giving them more contact time at the sites where they are most readily absorbed.

When a subject is in the digestive or "fed" mode, particulate matter above a certain minimum particle size is retained in the subject's stomach and remains there for the duration of the fed mode. The fed mode is distinguished from the fasting mode, which

prevails during nighttime rest and into the early morning hours. The fasting mode is characterized by interdigestive migrating motor complex (MMC) waves, which are a series of intense contractions beginning midway down the stomach and continuing down the intestinal tract to the distal ileum, clearing the stomach of digested materials as well as indigestible solids within a certain size range that would be retained if the stomach were in the fed mode. The fed mode is then initiated by the ingestion of food, and entails a suspension of the MMC waves, thereby permitting the stomach to retain the particulate matter long enough to break it down and at least partially digest it. When the the fed mode terminates, the MMC waves of the fasting mode resume but larger particulate matter is still retained by the stomach, the threshold size for the fasting mode being considerably larger than that for the fed mode.

The fed mode can be induced by the presence of food, possibly from either of two signals, one that is believed to stem from stomach distension and the other, a much stronger chemical signal, that is known to be based on nutrient and osmotic factors. These factors include hypertonic solutions, acid, fat, certain carbohydrates, and certain amino acids. Fat is the most powerful of these factors, relaxing the fundus with lower intragastric pressure, increasing the reservoir function of the proximal stomach, contracting the pyloric sphincter, and changing intestinal peristalsis from a propagated series of waves to segmenting activity.

Particles retained in the stomach due to their size could be a means of achieving prolonged retention in the stomach. The difference between the fasting and fed modes in terms of the minimum particle size that will be retained in the stomach is considerable, however, and particles large enough to be retained in the fasting mode are too large for practical administration in most patients. The lower minimum particle size of the fed mode therefore suggests that administering drugs during this mode could be both an effective and a feasible means of achieving retention of the drugs in the stomach.

While the fed mode is normally provided by ingestion of a meal, the use of a meal-induced fed mode as a means of prolonging the presence of a drug in the stomach has its disadvantages. One disadvantage is that the varying compositions of meals taken by different individuals make this approach unreliable. Another is that many drugs are adversely influenced by the presence of food in the stomach. Thus, while it increases the absorption of some drugs, it decreases the absorption of others.

Furthermore, use of the fed mode as a means of sustaining gastric retention requires that the drugs be formulated in particles of a size large enough to be retained. One can indeed ingest drugs in particles of this size, but it is still impractical in many cases to do so. The particles must retain their size while the drug dissolves in the gastric fluid so that dissolution of the drug does not by itself impair the controlled-release capabilities of the formulation. Also, the quantity of drug in the formulation should be

controllable independently of the particle size. There should be no need for example for the patient to ingest a large number of particles each of which is above the minimum size required for retention in the stomach.

The concern of administering and maintaining particles of appropriate size has been addressed by United States Patent No. 5,007,790 ("Sustained-Release Oral Drug Dosage Form," Shell, inventor, April 16, 1991). This patent discloses particle-form oral drug delivery systems in which the particles are small when taken orally but swell in the gastric fluid to approximately 8 to 11 mm, a size large enough to be retained in the stomach. Swelling to this size requires approximately two hours. Retention of the particles in the stomach while they are swelling requires that the patient be in the fed mode when the drug is administered, or at least that the swelling occur before the MMC waves of the fasting mode begin. With control of the MMC waves dependent on the timing of the fed mode and the manner in which the fed mode is induced, the system is subject to uncertainty, and the duration of the retention is at times, and in some individuals, less than desired.

SUMMARY OF THE INVENTION

The present invention resides in a sustained-release drug delivery system that combines the benefits of swellable particles with a pharmacologically induced fed mode to retain the drug delivery system in the stomach of the patient independently of the dietary habits or digestive cycles of the patient. Drug administration is thereby achieved with a high level of control over the site of drug delivery. The delivery system of this invention is a single dosage form for oral administration that includes both a solid-state drug dispersed or otherwise retained in a solid matrix of a water-swellable polymer, and a chemical agent that pharmacologically induces the fed mode. The water-swellable polymer matrix is in the form of particles that are small enough for oral administration yet rapidly swell upon imbibition of water from gastric fluid to a size sufficiently large that they are retained in the stomach for several hours even after the fed mode has passed and the MMC waves have resumed. The swollen particles maintain their size long enough to hold the particles in the stomach for the desired duration of drug delivery, which is generally in excess of several hours. The matrix may thus be susceptible to decomposition by the action of components in the gastric fluid, or it may tend to dissolve in the gastric fluid, but in either case at a rate slow enough to maintain the retention-promoting size of the matrix particles for the desired duration. The drug itself is soluble in the gastric fluid, yet is released from the matrix into the fluid at a limited rate due to the characteristics of the swollen matrix. The chemical agent inducing the fed mode is immediately released, at

least in part, to the gastric environment, thereby inducing the fed mode as soon as the dosage form reaches the stomach.

Details of these and other features of the invention will become apparent from the description that follows.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The water-swellable matrix that retains the drugs in accordance with this invention is any polymer that is non-toxic, swells in a dimensionally unrestricted manner upon imbibition of water, and provides for sustained release of an incorporated drug. Examples of these polymers are cellulose polymers and polyalkylene oxides.

The term "cellulose" is used herein to denote a linear polymer of anhydroglucose. Preferred cellulose polymers are alkyl-substituted cellulose polymers that ultimately dissolve in the gastrointestinal (G.I.) tract in a predictably delayed manner. The hydrophilicity and water swellability of these polymers cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water, and to become slippery, which further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate at which the drug diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the particle size and the drug concentration in the matrix. Correlatively, because these polymers dissolve very slowly in gastric fluid, the matrix particles maintain their integrity over at least a substantial period of time, *i.e.*, at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. In most cases, complete dissolution or decomposition will occur within 8 to 10 hours after the intended dosing period.

Preferred alkyl-substituted cellulose derivatives are those containing alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 6,500 centipoise as a 2% aqueous solution at 20°C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20°C. Particularly preferred alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Delaware, USA.

Polyalkylene oxides of greatest utility in this invention are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Preferred poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about 2×10^6 to about 8×10^6. Two presently preferred poly(ethylene oxide)s are POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Connecticut, USA, with a weight-average molecular weight of about 5×10^6.

The drug is preferably dispersed homogeneously in the polymeric matrix, although this is not a requirement of the present invention. The weight ratio of drug to polymer is not critical and may vary. In most cases, however, best results will be obtained with a weight ratio within the range of about 1:9 to about 9:1, preferably about 1:1 to about 9:1, and most preferably about 4:1 to about 9:1.

The particles are preferably consolidated into a packed mass for ingestion, even though they will separate into individual particles once ingested. Conventional methods can be used for consolidating the particles in this manner. For example, the particles can be placed in gelatin capsules known in the art as "hard-filled" capsules and "soft-elastic" capsules. The compositions of these capsules and procedures for forming them are known among those skilled in drug formulations. The encapsulating material should be highly soluble so that the particles are rapidly dispersed in the stomach after the capsule is ingested.

One presently preferred dosage form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, 6 mm in diameter and 10.5 mm in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.75 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 4.8 mm in length. These are merely examples; the shapes and sizes can be varied considerably.

The chemical agents that pharmacologically induce the fed mode in the patient's stomach generally fall into four classes: (1) serotonin receptor antagonists; (2) C_{10}-C_{15} fatty acids and salts thereof; and (3) L-tryptophan. Serotonin receptor antagonists are a known class of compounds. Examples are granisetron, dolasetron, ondansetron, tropisetron, zacopride, nazasetron, zatosetron, nexopamil, ketanserin, methysergide, 2-bromo-N,N-diethyl-D-lysergamide, pindobind, nefazodone, amesergide, and octreotide acetate. Of the fatty acids and their salts, those that are preferred are straight-chain saturated fatty acids, particularly the C_{12}-C_{14} acids. Preferred salts are the sodium and

potassium salts, with sodium particularly preferred. Thus, lauric acid, tridecylic acid, myristic acid, and the sodium salts of these acids are particularly preferred.

The fed-mode inducing agent is incorporated in the dosage form of this invention in such a manner that it induces the fed mode immediately upon ingestion. Accordingly, at least a substantial portion of the agent, and in many cases all of it, is released immediately upon contact with the gastric fluid. This result is preferably achieved by placing most, and preferably all, of the fed-mode inducing agent outside the water-swellable matrix rather than dispersing it in the matrix in the manner that the drug is dispersed. Thus, the agent is preferably layered or coated in solid form over the matrix, formed into one or more laminae of a laminated tablet in which the drug-impregnated matrix forms one or more other laminae, or added in powder form to a capsule that also contains the particles of water-swellable matrix.

The solid coating or layer preferably consists of the fed-mode inducing agent retained in a water-soluble matrix that rapidly disintegrates upon contact with the gastric fluid, thereby releasing the agent into the fluid. Examples of materials for such a matrix are sodium carboxymethylcellulose, sodium starch glycolate, crospovidone, hydroxypropylcellulose, and substituted hydroxypropylcellulose. Sodium starch glycolate is particularly preferred. The proportion of the fed-mode inducing agent in the water-soluble matrix can vary widely and is not critical. In most cases, however, best results will be achieved with a weight ratio of agent to total water-soluble matrix in the dosage form ranging from about 0.5:8 to about 3:5, and preferably from about 1:8 to about 2:8.

Since serotonin receptor antagonists are themselves therapeutic drugs, they can serve both their therapeutic function and the fed-mode inducement function when included in a dosage form of this invention. Accordingly, in dosage forms of this invention that include serotonin receptor antagonists the antagonists are preferably not immediately releasable upon contact with the gastric fluid, but held within the water-swellable matrix so that they are released at a controlled rate. The antagonist thus provides the benefits of gastric retention as well as its intended therapeutic function.

The amount of fed-mode inducing agent will vary depending on the type of agent used. In general, the amount will be selected as that which will induce and maintain the fed mode long enough for the particles of water-swellable polymer to reach a size which is large enough to be retained in the stomach in either the fed or fasting modes. Preferred amounts are within the range of about 50 mg to about 200 mg, and most preferably about 75 mg to about 150 mg, per single oral dosage form.

The dosage forms of this invention are effective for administering drugs of limited solubility in gastric fluid. The drugs include those that are capable of acting locally within the gastrointestinal tract or systemically by absorption into circulation by the gastrointestinal mucosa. Preferred drugs are solid and of limited water solubility to avoid

rapid diffusion of the drug from the water-swellable polymer matrix. To achieve this, it is preferred that portions of the drug be retained in the matrix in solid form for at least about two hours. Conversely, these drugs must be sufficiently soluble to permit the diffusion required to achieve the desired therapy. Thus, the solubility of the drugs should be such that they diffuse from the particles at a rate fast enough to provide an effective level of therapy yet slow enough to extend the treatment over the desired duration. In most cases, best results will be achieved with drugs whose solubility (determined in water at 37°C) lies within the range of about 0.01% to about 35% by weight, and preferably from about 0.1% to about 5% by weight.

The gastric retentive system of this invention is useful as a means of administering drugs to eradicate *Helicobacter pylori* from the submucosal tissue of the gastrointestinal tract, particularly the stomach. Such use of this gastric retentive system improves the effectiveness of these drugs against stomach and duodenal ulcers as well as gastritis and esophagitis, and for reducing the risk of gastric carcinoma. Drugs and drug combinations suggested for these indications include bismuth salts such as bismuth subsalicylate and bismuth citrate, metronidazole, and amoxycillin, other antibiotics such as clarithromycin, thiamphenicol, tetracycline, neomycin or erythromycin, and combinations of these drugs. Preferred drugs for this indication are clarithromycin plus omeprazole, a bismuth salt plus metronidazole, amoxycillin plus metronidazole, and amoxycillin or a bismuth salt plus omeprazole.

The invention can also be used with conventional ulcer treatment drugs such as the H-2 antagonists cimetidine or ranitidine, or a non-systemic antacid such as calcium carbonate. An antacid is often desirable as an additive to accompany agents that function most effectively in an anacidic stomach.

This invention is also of particular value in the administration of drugs such as peptides and proteins that are labile upon exposure to gastric pH or gastric enzymes. These drugs and others of a similarly large molecular size are most efficiently absorbed in the region extending from the lower stomach through the duodenum to the upper part of the small intestine. The formulations of this invention physically protect the undissolved portion of the drug within the water-swellable matrix until the drug dissolves and is thereby released. This results in continuous delivery of undegraded drug at or near this region of high absorptivity for an extended period of time. Therapeutic agents that otherwise require administration by injection can thus provide effective results when administered orally. Examples of such agents are calcitonin, calcitriol and insulin. Further examples of therapeutic agents that are not efficiently absorbed from the G.I. tract and that will therefore benefit from this invention are captopril, simvastitin, cyclosporins, acyclovir, cephalosporins, interleukins, nitrofurantoin, and the ergot alkaloids.

By delivering drugs in a continuous rather than pulse-wise manner as in conventional sustained-release dosage forms, the present invention offers both a reduction in side effects associated with the drug and the ability to achieve efficacy with less frequent administration. Examples of therapies in which this is useful are as follows:

(1) A reduction in angioedema and agranulocytoses, which are side effects arising from the administration of angiotensin-converting enzyme inhibitors such as enalapril maleate and captopril;

(2) A reduction of anti-cholinergic (drying) and sedative side effects of antihistamines such as clemastine fumarate;

(3) Prolonged activity for cholesterol lowering drugs such as lovastatin with less frequent administration and reduced side effects such as liver dysfunction, rhabdomyolysis, rash and headache;

(4) Prolongation of the effects of antidepressant agents such as fluoxetine, with a reduction of the side effects of insomnia and stomach upset;

(5) With the use of antiepileptic drugs such as carbamazepine, the benefit of only a single daily administration rather than administration three or four times a day as presently required, and a reduction of side effects;

(6) With potent analgesics such as meperidine, the benefit of steady, prolonged control of pain with reduced drug toxicity; and

(7) Less frequent administration, and irritation upon use of blood platelet aggregation inhibitors such as ticlopidine.

Similar benefits are obtained with other types of drugs. Calcium channel blockers, such as verapamil, diltiazem, nifedipine, or nicardipine, for example, can be administered with controlled delivery and gastric retention to extend their effects through the night and thereby alleviate early morning hypertension, the cause of many heart attacks. The frequency of administration can also be reduced to a single daily dose. Gastrointestinal prokinetic agents such as cisapride will similarly benefit from gastric retention. The invention also enhances the treatment of gastroesphageal reflux disease by providing prolonged, localized effects of agents such as pentagastrin, PG-F2, and metaclopramide that improves the competency of lower esophageal sphincter (LES) muscles.

Other drugs that will benefit from the invention include H-2 antagonists or calcium carbonate for ulcer treatment and prevention; non-steroidal anti-inflammatory agents (NSAIDS) such as indomethacin, ibuprofen, naproxen and piroxicam; steroids such as prednisone, prednisolone and dexamethasone; other NSAIDS such as diclofenac and ketorolac; acyclovir for the treatment of viral diseases such as herpes; tamoxifen for treatment of cancer; chlorpheniramine maleate for allergic disorders; potassium chloride for potassium supplementation, and peptides or other labile molecules such as protease

inhibitors for treatment of AIDS. Still further drugs will be apparent to those skilled in pharmacology.

The particulate drug/polymer mixture or drug-impregnated polymer matrix can be prepared by various conventional mixing and comminution techniques readily apparent to those skilled in the chemistry of drug formulations. Examples such techniques are as follows:

(1) Direct compression, using appropriate punches and dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pennsylvania, USA; the punches and dies are fitted to a suitable rotary tableting press, such as the Elizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pennsylvania, USA; and

(2) Injection or compression molding using suitable molds fitted to a compression unit, such as those available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.

When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the sphere) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight, preferably less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

Different drugs have different biological half-lives, and the frequency of administration needed for effective use of any single drug depends on the half-life of that drug. When two or more drugs are co-administered in a single dose using dosage forms of the prior art, an unfavorable compromise is often required, resulting in an underdose of one drug and an overdose of the other. The multi-particle dosage form of this invention permits different drugs to be placed in different matrix particles, each particle individually formulated to provide the release rate and duration that are optimal for the particular drug carried by that particle. This can be done by varying the matrix composition, the particle size, the particle molecular weights, or any other characteristic that affects the release rate and duration. The number of particles carrying individual drugs can also be varied among the different drugs. For example, a capsule made from three particles may contain two particles carrying one drug and one particle carrying the other drug.

Examples of drug combinations for which the formulations of this invention are useful are norethindrone plus ethinyl estradiol, a combination useful for fertility control, acetaminophen plus codeine (a potent analgesic combination), captopril plus

hydrochlorthiazide (a useful cardiovascular combination), and clarithromycin plus omeprazole (for the eradication of *H. pylori*). In these and other examples, each ingredient can be individually formulated to achieve a release rate that is optimal for the pharmacokinetics and biological activity of each drug. This invention is also useful as a means of co-administering drugs that cannot otherwise be combined in a single dosage form due to their chemical incompatibility.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, proportions, methods of formulation and other parameters of the system described herein may be further modified or substituted in various ways without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A sustained-release oral drug single dosage form for releasing a drug into the stomach, comprising:

a solid-state drug retained in a solid matrix of a water-swellable polymer; and

a chemical agent that promotes retention of substances in the stomach by pharmacologically inducing the fed mode.

2. A sustained-release oral drug single dosage form in accordance with claim 1 in which said chemical agent is a member selected from the group consisting of serotonin receptor antagonists, L-tryptophan, C_{10}-C_{15} fatty acids, and salts of C_{10}-C_{15} fatty acids.

3. A sustained-release oral drug single dosage form in accordance with claim 1 in which said chemical agent is a serotonin receptor antagonist.

4. A sustained-release oral drug single dosage form in accordance with claim 3 in which said serotonin receptor antagonist is a member selected from the group consisting of granisetron, dolasetron, ondansetron, tropisetron, zacopride, nazasetron, zatosetron, nexopamil, ketanserin, methysergide, 2-bromo-N,N-diethyl-D-lysergamide, pindobind, nefazodone, amesergide, and octreotide acetate.

5. A sustained-release oral drug single dosage form in accordance with claim 1 in which said chemical agent is L-tryptophan.

6. A sustained-release oral drug single dosage form in accordance with claim 1 in which said chemical agent is a member selected from the group consisting of C_{10}-C_{15} fatty acids and salts of C_{10}-C_{15} fatty acids.

7. A sustained-release oral drug single dosage form in accordance with claim 6 in which said chemical agent is a member selected from the group consisting of straight-chain saturated C_{10}-C_{15} fatty acids and sodium and potassium salts thereof.

8. A sustained-release oral drug single dosage form in accordance with claim 6 in which said chemical agent is a member selected from the group consisting of lauric acid, tridecylic acid, myristic acid, and sodium salts thereof.

9. A sustained-release oral drug single dosage form in accordance with claim 1 in which said water-swellable polymer is a member selected from the group consisting of cellulose polymers and polyethylene oxide.

10. A sustained-release oral drug single dosage form in accordance with claim 1 in which said water-swellable polymer is a member selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, and polyethylene oxide.

11. A sustained-release oral drug single dosage form in accordance with claim 1 in which said water-swellable polymer is a member selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, and polyethylene oxide.

12. A sustained-release oral drug single dosage form in accordance with claim 1 in which said chemical agent is in a solid coating adhering to a surface of said solid matrix.

13. A sustained-release oral drug single dosage form in accordance with claim 12 in which said solid coating is comprised of said chemical agent suspended in a water-soluble matrix.

14. A sustained-release oral drug single dosage form in accordance with claim 13 in which said water-soluble matrix is a member selected from the group consisting of sodium carboxymethylcellulose, sodium starch glycolate, crospovidone, hydroxypropylcellulose and substituted hydroxypropylcellulose.

15. A sustained-release oral drug single dosage form in accordance with claim 13 in which said water-soluble matrix is sodium starch glycolate.

16. A sustained-release oral drug single dosage form in accordance with claim 1 in which said chemical agent comprises from about 50 mg to about 200 mg of said oral dosage form.

17. A sustained-release oral drug single dosage form in accordance with claim 1 in which said solid state drug comprises from about 200 mg to about 2000 mg of said oral single dosage form, and said chemical agent comprises from about 50 mg to about 200 mg of said oral single dosage form.

18. A sustained-release oral drug single dosage form in accordance with claim **1** in which said solid state drug comprises from about 300 mg to about 1200 mg of said oral single dosage form, and said chemical agent is a member selected from the group consisting of C_{10}-C_{15} fatty acids and salts of C_{10}-C_{15} fatty acids and comprises from about 75 mg to about 150 mg of said oral single dosage form.

19. A sustained-release oral drug single dosage form in accordance with claim **1** in which said solid state drug is a member selected from the group consisting of *Helicobacter pylori* eradicants, potassium chloride, peptides, cisapride, calcium carbonate, bismuth subsalicylate, captopril, and simvastitin.

20. A sustained-release oral drug single dosage form in accordance with claim **1** in which said solid state drug is a *Helicobacter pylori* eradicant selected from the group consisting of amoxycillin, a bismuth salt plus omeprazole, a bismuth salt plus an H-2 antagonist, a bismuth salt plus an antacid, and clarithromycin plus omeprazole.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 163 648 A (NIPPON SHINYAKU) 5 March 1986	1,2, 6-11, 13-20
Y	see claim 1 see page 1, line 60 - page 2, line 10 see page 2, line 19 - line 25 see page 3, line 5 - line 6 ---	3,4
X	EP 0 497 977 A (NIPPON SHINYAKU) 12 August 1992	1,2, 6-11, 13-20
Y	see claim 1 see column 4, line 4 - line 27 see column 4, line 47 - column 5, line 2 see column 6, line 5 - line 8 --- -/--	3,4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 1997	15.10.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/09245

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 272 876 A (GLAXO GROUP LIMITED) 29 June 1988 see page 8, line 55 - page 9, line 4 see page 9, line 34 - line 37 see page 11, line 25 - line 50	3,4
A	WO 93 18755 A (DEPOMED SYSTEMS) 30 September 1993 see the whole document	1-20
A	US 4 659 558 A (ALZA CORPORATION) 21 April 1987 see column 4, line 3 - line 63	1-20
A	EP 0 391 462 A (JANSSEN PHARMACEUTICA) 10 October 1990 see page 4, line 24 - line 34 see examples 2,3	4,19
A	EP 0 477 625 A (E.R. SQUIBB & SONS) 1 April 1992 see page 4, line 19 - line 28 see examples 3,4	4,19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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